

REMARKS/ARGUMENTS AND INTERVIEW SUMMARY

Applicants thank the Examiner for conducting a telephone interview on August 17, 2004 at which the outstanding office action and certain claim amendments were discussed. The Examiner agreed that claim 37 as it stood was distinguished over the art. The discussion is referred to below, as relevant, in responding to the comments in the office action.

Claims 35, 37, 38, 40-43, 48, 49, 52 and 53 are pending and have been examined. Claims 1-34, 36, 44-47, 50 and 51 were previously canceled, and claim 39 is canceled herewith. Support for the amendment to claim 35, 48, 49 and 53, reciting that at least one protein in the database has a third finger that is different from the third finger of at least one other protein in the database, is provided by Table 9 (specification at p. 58). As noted in the specification at p. 30, line 16, Table 9 illustrates the organization of a typical database of the invention. Claim 37 has been rewritten in independent form including the elements from antecedent claim 38. Claims 42 and 43 have been amended to include an additional step of identifying subsets of the sets of zinc fingers. This step is analogous to step (d) of claim 37, and as described in the specification at e.g., p. 31, lines 10-17, and the paragraph bridging pp. 32-33. All independent claims have been amended to remove the term "new" as requested by the Examiner. Claims 35, 37, 42 and 43 have been amended to recite methods of producing zinc finger proteins *or nucleic acids encoding the same*. Such is supported by the specification at e.g., p. 33, lines 11-12. No claim amendment should be construed as an acquiescence in any ground of rejection.

Minor amendments have been made to certain figures to correct typographic errors in production of the previously submitted formal drawings. The corrections are supported by the informal drawings as filed.

Applicants now address the comments in the office action using the paragraph numbering of the office action.

2-3. The term "new" has been deleted from the claims so the rejection relating to this term is moot.

The expression "null set" was explained in the interview as meaning a subset of zinc finger proteins (as recited in claim 37) having zero members. In view of the rewriting of claim 37 in independent form, claim 39 is redundant and has been cancelled.

10-11. Claim 53 stands rejected as unpatentable over Desjarlais. At the interview, the Examiner clarified that Desjarlais was being applied specifically to claim 53 because applicants had not amended this claim to recite that the zinc finger proteins in the database were precharacterized. Such an amendment has been made in this response. Applicants note for the record that they maintain the claims are distinguished over Desjarlais for several other reasons, as outlined in previous responses, and respectfully disagree with the Examiner's other comments regarding Desjarlais. However, these issues are moot in view of the noted amendment, which the Examiner said would overcome the rejection.

12. Claims 35, 37, 38, 40, 42, 43, 48, 49 and 53 stand rejected under 35 USC 103(a) as obvious over Choo (1994b), in view of Choo (1994a). Choo (1994b) is alleged to disclose selection of zinc fingers from a randomized library for binding to a desired triplet and combination of the selected zinc fingers into three-finger zinc finger proteins as shown in Fig. 2 of the reference. The Examiner acknowledges that Choo (1994b) does not explicitly show that the randomized library of zinc finger proteins consists of three-finger zinc finger proteins, the extent of precharacterization of the proteins in the randomized zinc finger library, a database of the randomized zinc finger library, or a computer-mediated method. Choo (1994a) is cited as disclosing a phage library in which the middle finger of a three-finger protein is randomized, and, in Fig. 2, a database of selected and characterized library members. The Examiner takes the view that it would have been obvious to precharacterize the selected random library members of Choo (1994b) to aid in further analysis of selected library members, because Choo (1994a) shows such analysis. The Examiner takes the view that it would have been obvious to record such characteristics in a database as shown in Figure 2 of Choo (1994a), and to automate use of the same with computers. This rejection is respectfully traversed, particularly as it might be applied to the amended claims.

Choo (1994b) discusses an experiment to design a zinc finger protein to bind to a single preselected target sequence (5'GCA GAA GCC3'). As was discussed at the interview, the sequences shown in Fig. 2 of Choo (1994b) are of single fingers of a zinc finger proteins. Choo (1994b) indicates that these fingers were selected by the method of Choo (1994a). In this method, a randomized middle finger is flanked by first and third constant fingers from the natural protein Zif268. The first and third constant fingers bind to the respective triplets in the natural Zif268 target site (5'GCG TGG GCG3') and thus are not relevant to Choo (1994b)'s goal of designing a zinc finger protein to bind to the target site 5'GCA GAA GCC3'. Thus, in applicants' view, there would have been no motivation to include these flanking fingers in a database for design of Choo (1994b)'s intended protein.

Nevertheless, in accordance with the discussion at the interview, claims 35, 48, 49 and 53 have been amended to specify that precharacterized zinc finger proteins in the database of the present claims differ among each other at least in finger three of a three-finger zinc finger protein. Such is distinct from the zinc finger proteins which apparently gave rise to the zinc fingers in Fig. 2 of Choo (1994b). Such is also distinct from the zinc finger proteins discussed by Jamieson *et al.*, Proc Natl. Acad. Sci. USA. 93(23):12834-9 (1996), a reference mentioned by the Examiner during the interview.

It is respectfully submitted that there was no motivation to modify the teaching of Choo (1994b) or (1994a) by randomizing the third finger of a zinc finger protein, including the resulting randomized proteins in a database, and then applying steps (b)-(e) recited in the present claims. As noted, the Choo references use the first and third fingers as a framework to facilitate selection of middle fingers. The middle fingers are then used in all positions (*i.e.*, first, middle and third fingers) of Choo's final zinc finger protein. The two cited references do not disclose any advantages of randomization of the first or third fingers in Choo's scheme, in which zinc finger proteins are produced by combination of randomized middle fingers alone. Accordingly, it is respectfully submitted that amended claims 35, 48, 49 and 53 are not suggested by the Choo references.

Claim 37, as previously pending, and claims 42 and 43 as amended are distinguished on additional grounds. As was discussed at the interview, claim 37 (and claims 42

and 43, as amended to include a step (d) analogous to that of claim 37) are directed to a design method which uses information on the position of the zinc fingers in the precharacterized zinc finger proteins in the database. Specifically, claim 37 requires a step of identifying subsets of zinc finger protein(s) based on both the binding specificity of a zinc finger and the position in the protein from which the zinc finger binds its triplet subsite. As noted in the specification (see, e.g., p. 29, lines 26-30), such is advantageous because when the environment of each finger in a designed zinc finger protein is analogous to its environment in the precharacterized zinc finger protein in the database, it is likely to bind with similar specificity and affinity in the designed zinc finger protein as it did in the precharacterized protein. By contrast, both Choo (1994a) and Choo (1994b) propose the use of a middle zinc finger from selected zinc finger proteins to occupy each position of his designed zinc finger protein; and lack any teaching to select subsets of zinc finger proteins as recited in step (d) of claim 37, and analogous steps (d) of claims 42 and 43, or produce a zinc finger protein from the fingers of zinc finger proteins occupying such subsets as recited in steps (f) of these claims.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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Attachments
JOL:jol
60299201 v1

Appl. No. 09/825,242
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Reply to Office Action of July 2, 2004

PATENT

Amendments to the Drawings:

The attached sheet of drawings includes changes to Figs. 1, 2, 7B and 8B. The replacement sheets replace the original sheets.

Attachment: Replacement Sheets
Annotated Sheet Showing Changes



Kd of Designed ZFPs vs. D-able Site / Target:
Affinity is a function of number and type of D-able site

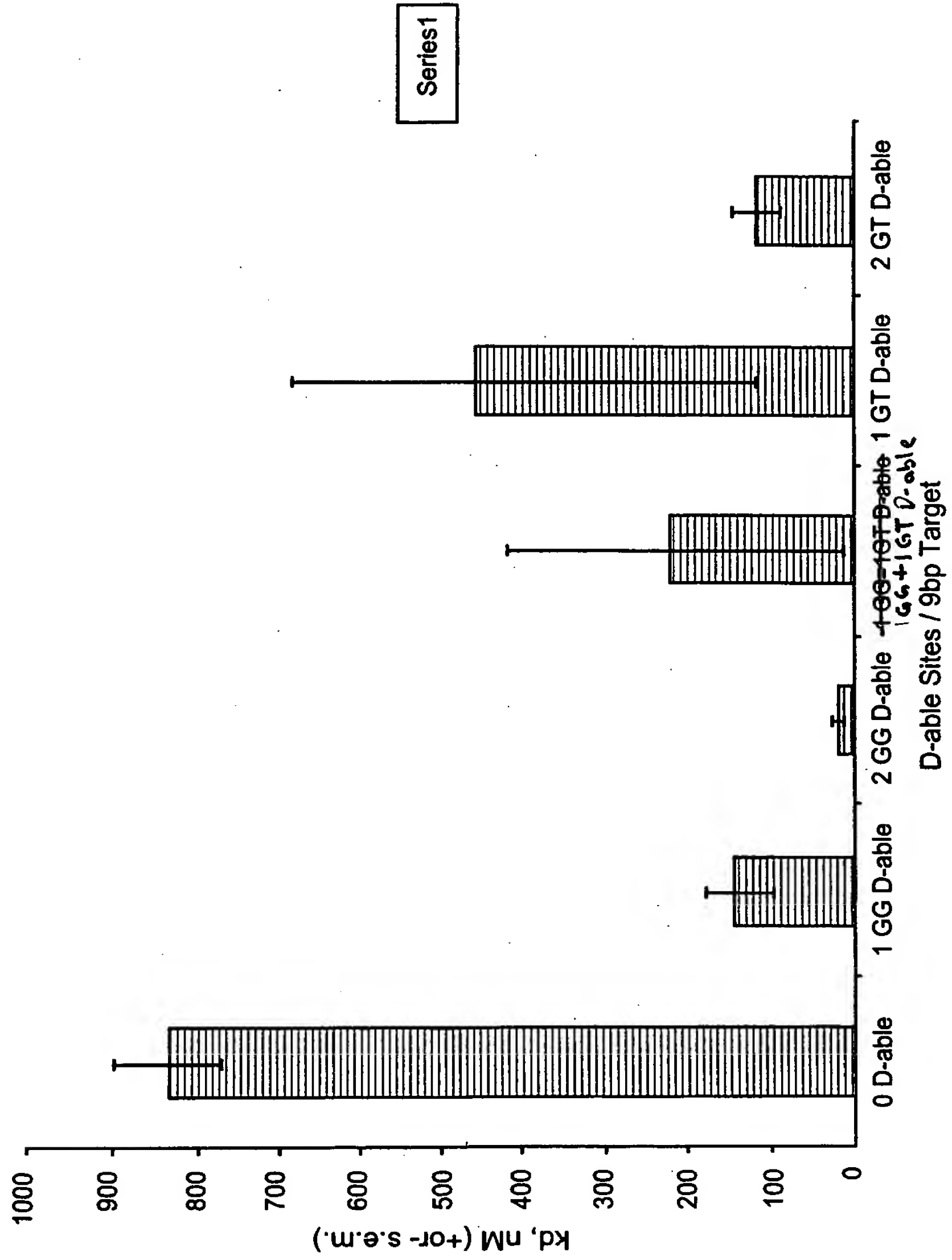
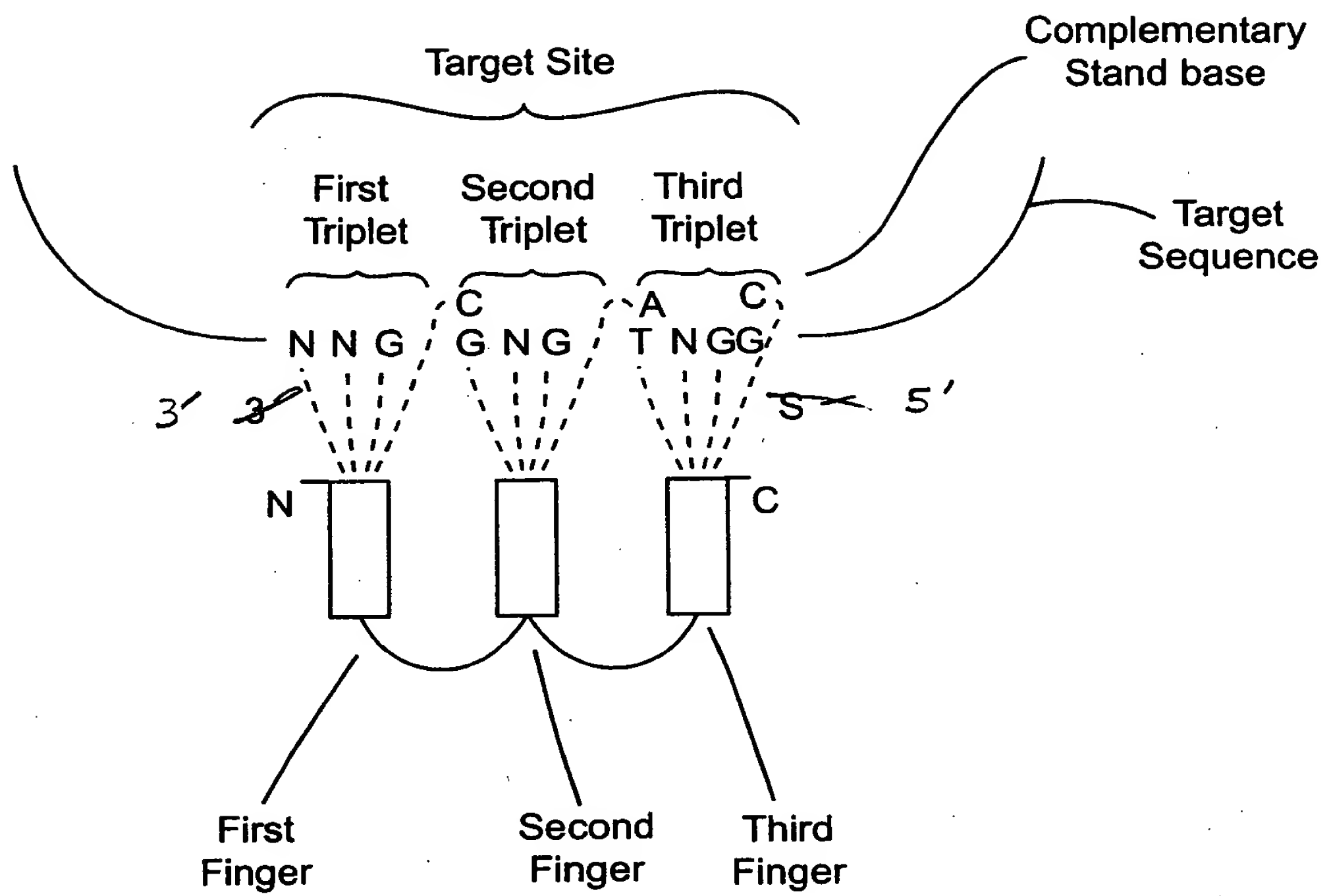
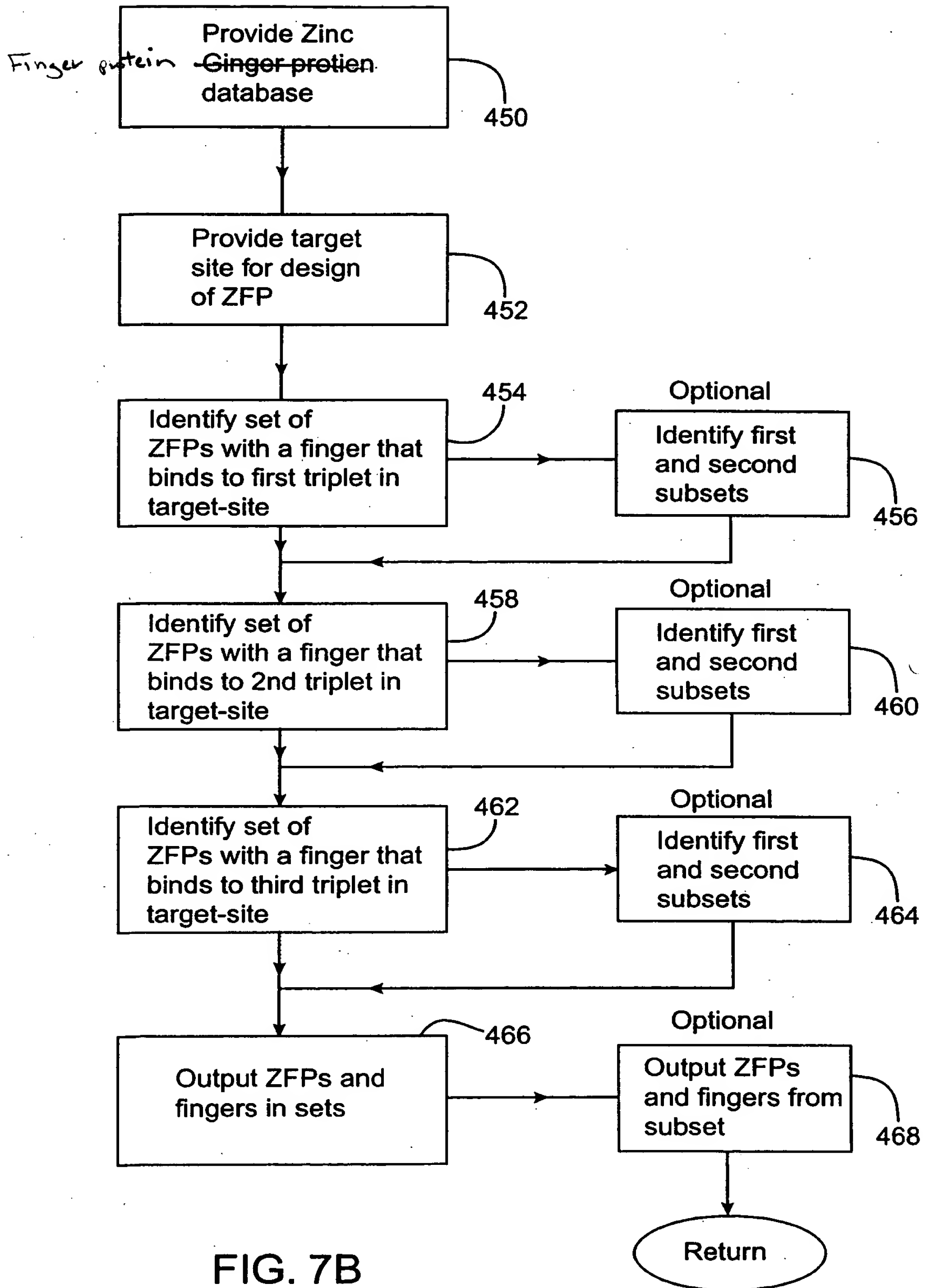
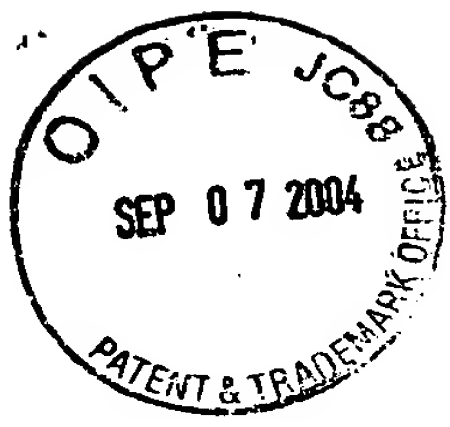


FIG. 1







10 / 10

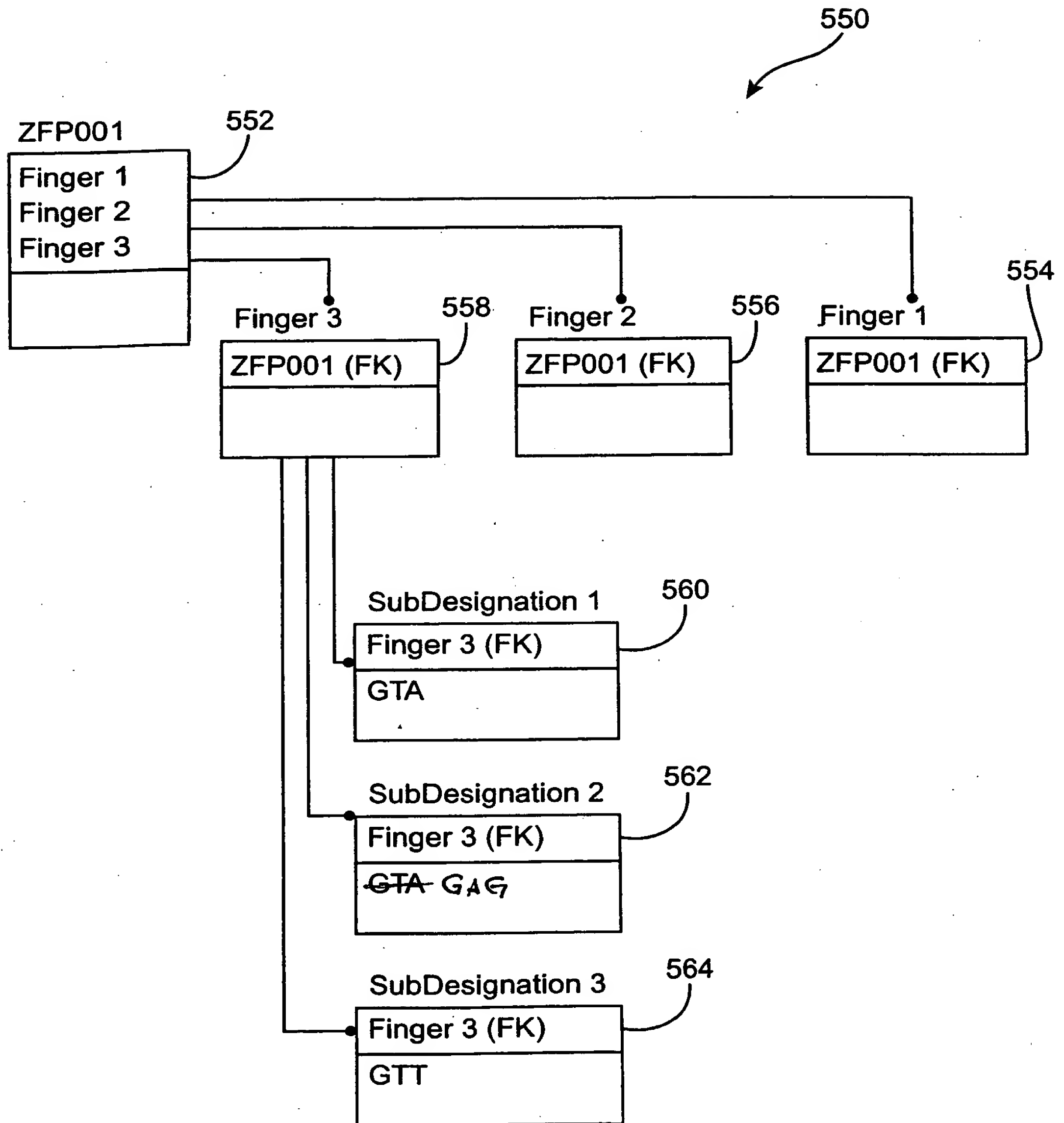


FIG. 8B